SUPPLEMENTAL DATA

RyR_2^{R420Q} Catecholaminergic Polymorphic Ventricular Tachycardia mutation induces bradycardia by disturbing the coupled clock pacemaker mechanism

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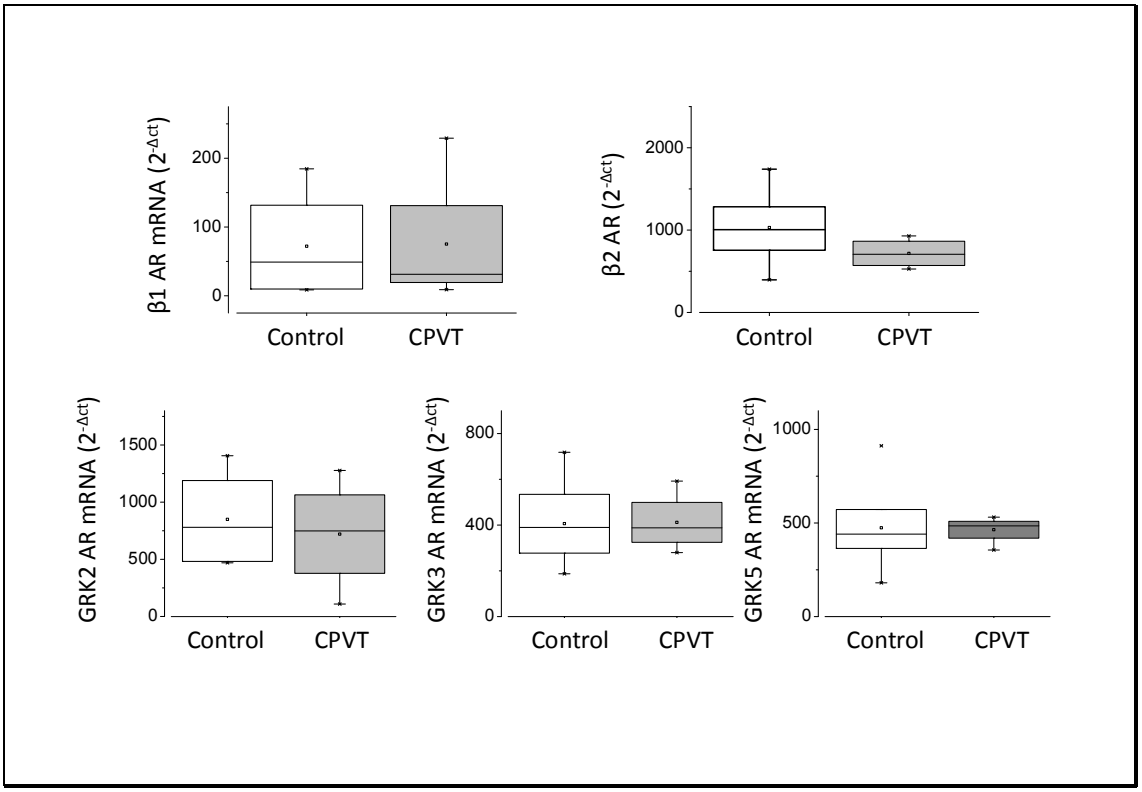
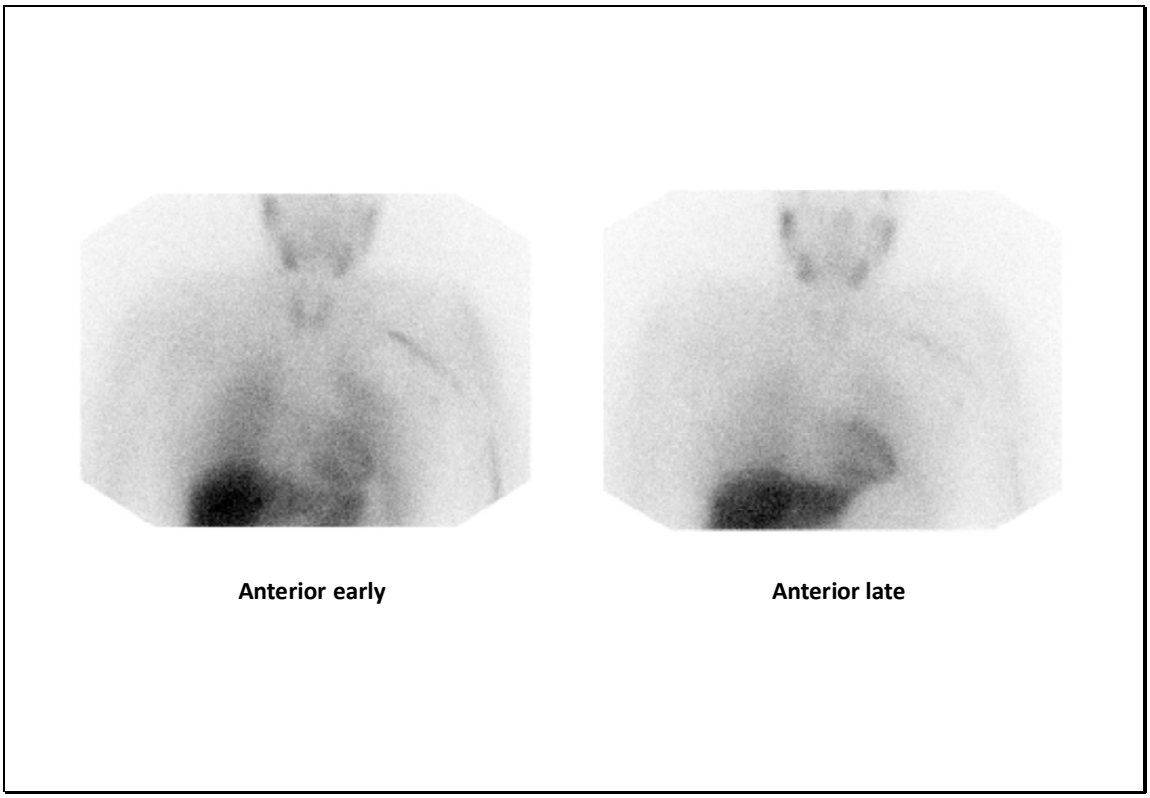
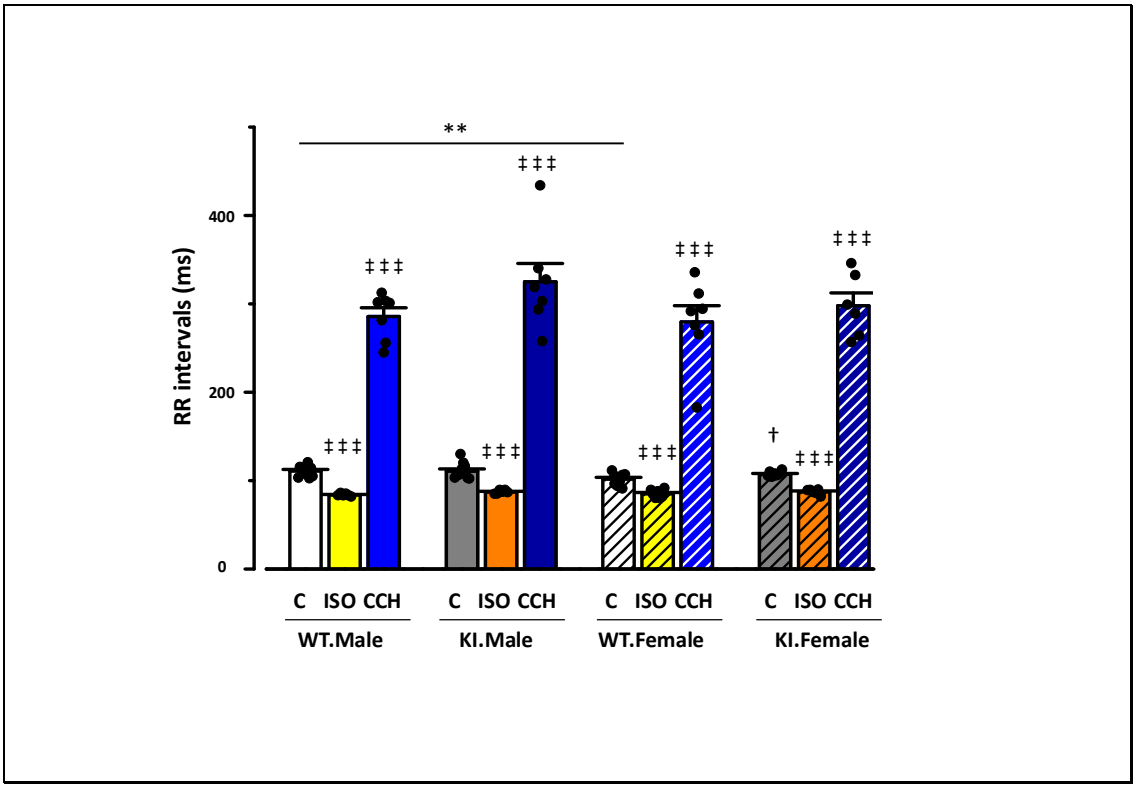


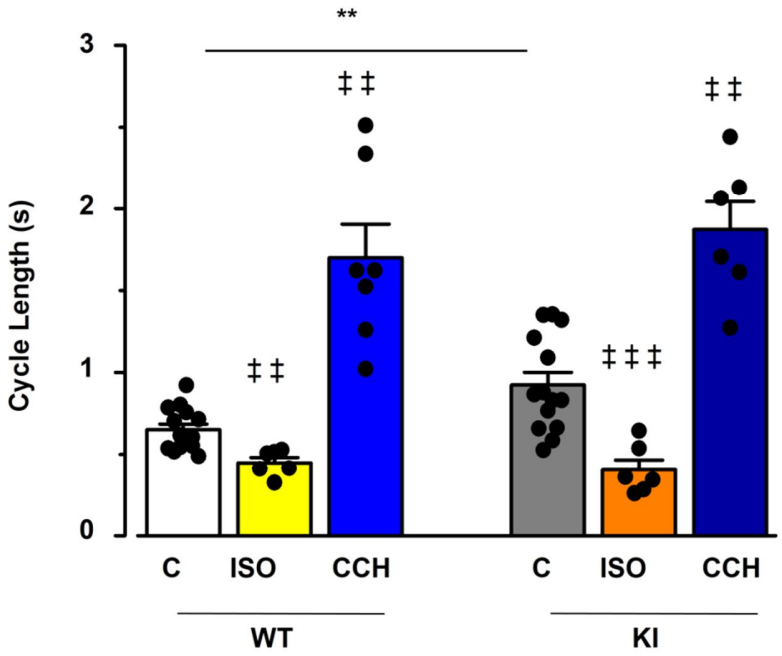
Supp. Fig.1. **β adrenergic receptors and β adrenergic receptor kinases expression are normal in RyR_2^{R420Q} CPVT patients**. From left to right and from top to bottom, mRNA levels for β_1 and β_2 adrenergic receptors (ARs) and G protein receptor kinases (GRK) GRK2, GRK3 and GRK5 measured in the peripheral blood mononuclear cells obtained from healthy volunteers (white bars, N=8) or CVPT patients (gray bars, N=4). The Ct values obtained for each gene were referenced to *GAPDH* and converted into the linear form using the term $2^{-\Delta Ct}$ x 10000 as a value directly proportional to the mRNA copy number. Data presented as box chart with 25-75% percentiles. Independent sample t-test was performed but no significant differences were found between groups (P>0.05).



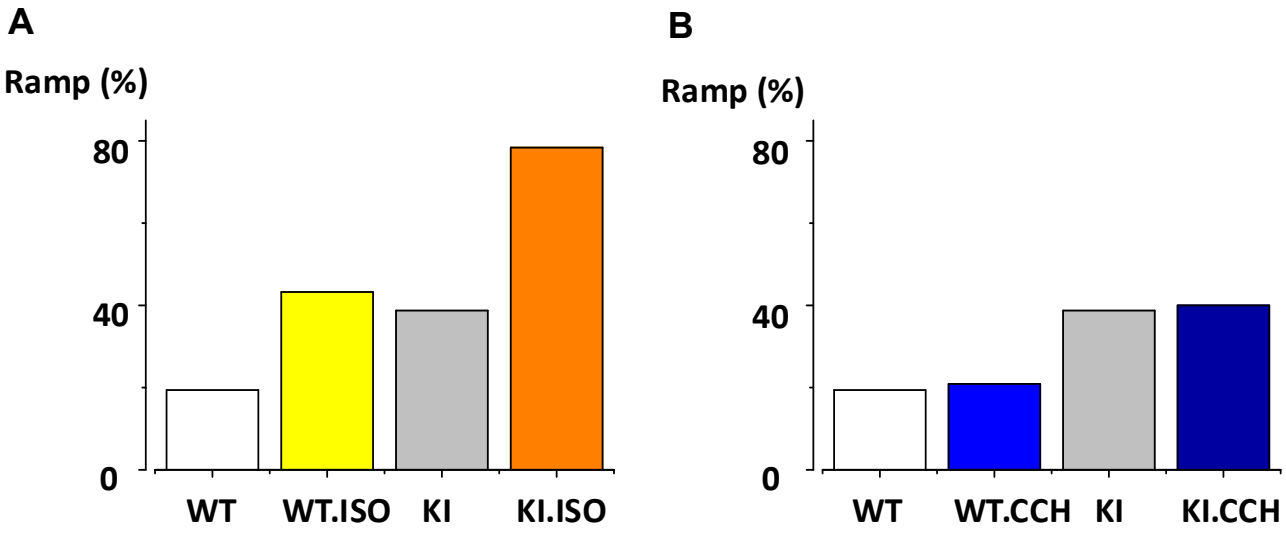
Supp. Fig. 2. **Representative planar images from the anterior projection of a CPVT patient carrier of the RyR_2^{R420Q} mutation**. The H/M ratio (Heart/Mediastinum Count Ratio) and WR (washout rate) parameters are not altered. Anterior early H/M: 1.75, anterior late H/M: 1.7, WR: 20%



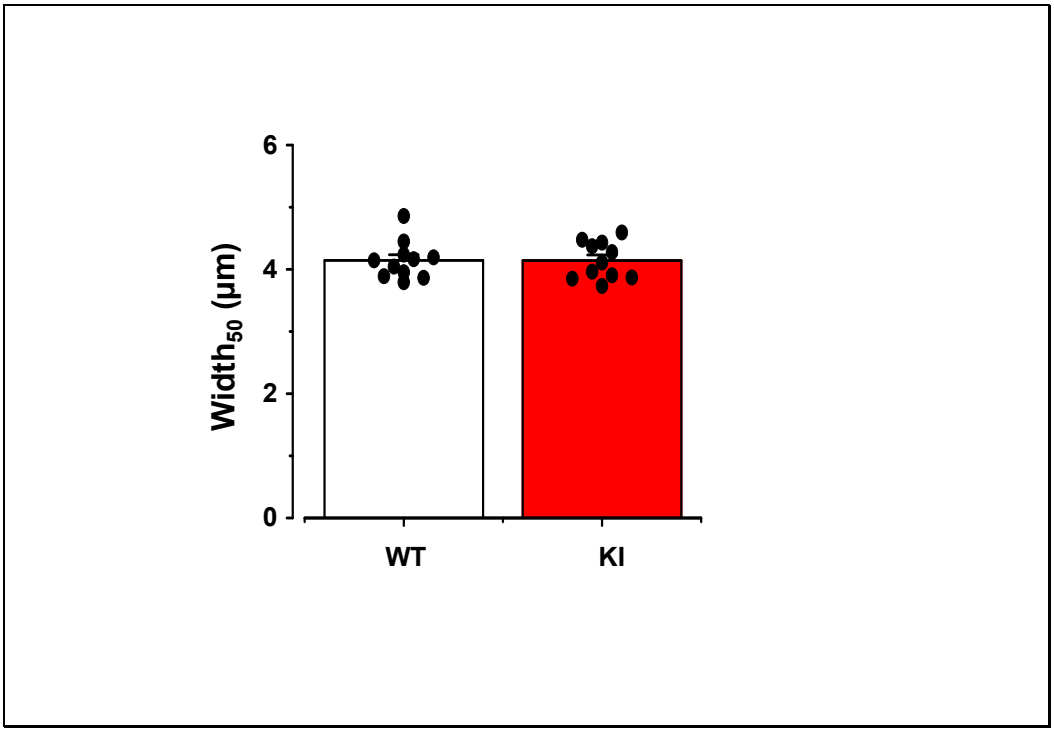
Supp. Fig. 3. Absolute values of RR intervals in vivo in wild type (WT) and RyR_2^{R420Q} (knock in, KI) mice. RR interval in vivo before (C, white and grey for WT and KI respectively) and after 1mg/kg isoproterenol i.p. injection (ISO) (yellow and orange for WT and KI respectively) or 0.25mg/kg carbachol i.p. injection (CCH) (blue and navy blue for WT and KI respectively) challenge in WT and KI mice. Bars with diagonal stripes represent females. N values are the same as Figure 1. ***P*<0.01 vs. WT male. †*P*<0.05 vs. WT female, ‡‡‡ *P*<0.0001 vs. basal condition.



Supp. Fig.4. Absolute value of cycle length in intact sinoatrial node before and after isoproterenol (ISO) or carbachol (CCH) challenge. White and grey represent basal wild type (WT) and knock-in (KI) respectively, and yellow and orange WT and KI after ISO repsectively, while blue and navy blue are WT and KI after CCH challenge. The SAN (sino atrial node) and cell numbers are the same than in Figure 3. **p<0.01 with respect to WT, ‡‡ *P*<0.01 and ‡‡‡ *P*<0.001 with respect to basal conditions.



Supp. Fig. 5. Ramp occurrence in the presence of isoproterenol (ISO) or carbachol (CCH). **A**. Ramp occurrence is increased by ISO application in both wild type (WT) and knock-in (KI) sinoatrial node cells. From 102 WT cells (15 mice) and 81 KI cells (14 mice) in basal condition, and 44 WT cells (7 mice) and 40 KI cells (6 mice) after ISO stimulation. **B**. Ramp occurrence is unchanged after CCH stimulation, from 102 WT cells (15 mice) and 81 KI cells (14 mice) in basal condition; 67 WT cells and 55 KI cells after CCH stimulation.



Supp. Figure 6. Ca^{2+} spark width is unaltered in knock-in (KI) sinoatrial node cells compared to wild type (WT). The $Width_{50}$ was measured when the spark fluorescence trace is at 50% of maximum peak. Each point is the value for one sinoatrial node, n as in Figure 7.